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Coronary Heart Disease and Migration: Management, Prognosis and Health Equity

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Abstract

Background and aim: Coronary heart disease (CHD), the most common form of which is myocardial infarction (MI), is a significant health problem. In Sweden circulatory diseases account for 50% of total mortality; half of these are associated with CHD. The percentage of foreign-born in Sweden is about 16 % of the total population. Ethnic differences in disease and its outcomes have been widely reported internationally. This thesis was to increase understanding of the differences in utilization of health care by exploring the incidence and recurrence of MI, drug consumption after MI, prognosis after MI and coronary artery bypass graft (CABG) in relation to country of birth, socio-economic position (SEP) and gender.

Materials and methods: The data used in this thesis are from newly established Migration and Health Cohort specifically designed to address health status among immigrants in Sweden. The cohort is a linkage of several national registers. There were four studies. The study periods were 1987–2008 (Study I), 2006–2008 (Study II), 1987–2007 (Study III) and 1995 – 2007 (Study IV). The study populations were the total Swedish population (Study I), all first MI patients (Studies I, II and III) and all individuals who underwent a first isolated CABG (Study IV). The outcomes were incidence of and mortality after MI (Study I), drug use after MI (Study II), recurrent MI (Study III) and mortality after CABG respectively (Study IV). The potential confounders were age, sex, education, comorbidities, calendar years of follow-up, marital status and waiting time for surgery. We calculated incidence rate ratios (IRRs) and hazard ratios (HRs) (Studies I, III and IV) and odds ratios (ORs) (Study II) with 95% confidence intervals (CIs) in multivariable adjusted models using Poisson, Cox, and logistic regression models, respectively.

Results: We observed downward trends in first-time MI incidence and case fatality after day 28 for both sexes regardless of country of birth. The trends were, however, less pronounced among female and foreign-born subjects. Among those who did not used cardiovascular drugs before MI, we found no difference in drug use after MI by migration status in an adjusted model (OR 1.00, 95 % CI 0.89–1.12). Among those who used some but not all recommended cardiovascular drugs before MI, foreign-born cases had a non-significant slightly lower use of recommended drugs in the adjusted model (OR 0.92, 95 % CI 0.83–1.03). Among those with the lowest education level, foreign-born patients had a slightly lower use of recommended drug compared to Sweden-born patients. Women with a low SEP used fewer drugs after MI irrespective of country of birth (Study II). A downward trend in risk of second MI was found. However, regardless of country of birth, men had a higher risk of second MI than women (HR 1.14, 95% CI 1.12–1.55). Foreign-born men and women had a slightly increased HR than their Sweden-born counterparts. Foreign-born patients who had lived in Sweden for less than 35 years had a higher risk than those who had lived there for 35 years or longer (Study III). There was no significant difference in overall early or late mortality after CABG between foreign-born and Sweden-born patients in both sexes. However, all-cause mortality differed between some countries and was highest in foreign-born men from Eastern Africa (HR 3.80, 95% CI 1.58–9.17), China (HR 3.61, 95% CI 1.50–8.69) and Chile (HR 2.12, 95% CI 1.01–4.47) (Study IV). Patients with a low level of education had higher incidence of MI and worse prognosis after MI and CABG compared to those with longer than 12 years of education irrespective of sex and country of birth (Studies I, III and IV). This difference was more pronounced among foreign-born women.

Conclusion: A slightly increased incidence of and mortality after first MI, and risk of recurrent MI was found among foreign-born compared to Sweden-born individuals. Although the incidence of and mortality after first-time MI, and risk of recurrent MI, continued to decrease over time, low SEP, measured in terms of education level, independent of country of birth and sex, remained an important risk indicator for these events. There were no apparent differences in drug prescription after MI between foreign-born and Sweden-born patients. There were no differences in early and late mortality after isolated CABG. However, there was inequity in adequate secondary prevention therapy after MI between education groups regardless of country of birth.

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CORONARY HEART DISEASE AND MIGRATION: MANAGEMENT, PROGNOSIS AND HEALTH EQUITY

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Karolinska Institutet

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In the name of God, the Merciful, the Compassionate

To my mother and father

Rezheen, and Zhiwa

my family

my uncle Saadi Sinjawi

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LIST OF SCIENTIFIC PAPERS

Study I Dong Yang , **Dashti Ali Mustafa Dzayee**, Omid Beiki, Ulf de Faire, Lars Alfredsson, Tahereh Moradi. Incidence and case fatality after day 28 of first time myocardial infarction in Sweden 1987-2008. Eur J Prev Cardiol. 2012 Dec;19(6):1304-15.

Study II **Dashti Ali Mustafa Dzayee**, Tahereh Moradi, Omid Beiki, Lars Alfredsson, Rickard Ljung. Recommended drug use after acute myocardial infarction by migration status and educational level. Manuscript

Study III **Dashti Ali Mustafa Dzayee**, Omid Beiki, Rickard Ljung , Tahereh Moradi. Downward trend in the risk of second myocardial infarction in Sweden, 1987-2007: breakdown by socioeconomic position, gender, and country of birth. Eur J Prev Cardiol. 2014 May;21(5):549-58.

Study IV **Dashti Ali Mustafa Dzayee**, Torbjörn Ivert, Omid Beiki, Lars Alfredsson, Rickard Ljung, Tahereh Moradi. Short and long term mortality after coronary artery bypass grafting (CABG) is influenced by socioeconomic position but not by migration status in Sweden, 1995-2007. PLoS One. 2013;8(5):e63877.

CONTENTS

LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
ACE	Angiotensin Converting Enzyme Inhibitor
AHA	American Heart Association
AMI	Acute myocardial infarction
ATC	Anatomical therapeutical chemical
APC	Annual percent change
ARIC	Atherosclerosis Risk in Communities
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CHD	Coronary heart disease
CI	Confidence interval
CVD	Cardiovascular disease
ECG	Electrocardiogram
ESC	European Society of Cardiology
HR	Hazard ratio
ICD	International Classification of Diseases
IHD	Ischemic heart disease
IPR	Inpatient register
IRR	Incidence rate ratio
LDL	low density lipoprotein
LISA	Longitudinal integration database for health insurance and labor market studies
MI	Myocardial infarction
NPR	National Patient Register
NSTEMI	Non-ST-elevation MI
OR	Odds ratio
OTC	Over-the-counter drugs
PCI	Percutaneous coronary interventions
PIN	Personal identity number
RIKS-HIA	Register of Information and Knowledge about Swedish Heart Intensive Care Admissions
SCAAR	Swedish Coronary Angiography and Angioplasty Registry
SCORE	System for Cardiac Operative Risk Evaluation
SEP	Socio-economic position
SHEEP	Stockholm Heart Epidemiology Program
STEMI	ST-elevation MI
TPR	Total populations register
WHO	World Health Organization

1 INTRODUCTION

Coronary heart disease (CHD), the most common form of which is myocardial infarction (MI), is the main component of cardiovascular disease (CVD). CVD is a universal public health problem and considered to be a major cause of deaths worldwide. In 2008, of a total of 17.3 million cardiovascular deaths, 7.3 million were due to heart attacks. CVD accounts for more than 4 million deaths in Europe each year, or which 1.8 million are due to CHD (1-3). CHD remains the leading cause of death in high- and middle income countries and is predicted to be the leading cause worldwide within a few decades (4). In Sweden, CVD is the most common cause of death in both sexes. The burden of CVD is an important issue in Sweden. In 2010, CVD was the primary cause of death in 40% of cases, and CHD accounted for 42% of cardiovascular deaths (5, 6).

The rise in international migration has made the subject of health among immigrants increasingly important worldwide. In Sweden about 16 % of the population, approximately 1.5 million individuals, are born outside Sweden (7).

Depending on ethnicity (8-13), socioeconomic position (SEP) (14-19), and sex (20, 21), there are differences in the incidence, morbidity, prognosis and mortality after MI. There are some indications that access to health care services and health care utilization is influenced by country of birth, SEP, and sex (10, 13, 22-28). Ethnic differences in health care have been widely reported internationally. Whites seem more likely than other ethnic groups to undergo cardiovascular procedures such as angiography, angioplasty and coronary artery bypass graft (CABG) after MI in the United States (13, 23). Studies exploring access to health care including interventional services for MI patients are important. Prescribed drugs, surgical interventions, re-occurrence of disease, survival are a few examples of measures that can be assessed to compare differences in access to and consumption of health care among different populations.

2 BACKGROUND

2.1 IMMIGRATION TO SWEDEN

The pattern of emigration from and immigration to Sweden has changed dramatically over the past decades. Sweden had a net emigration during 1930s and World War I but become a country of net immigration since the World War II (29).

The total population of Sweden as of 31 December 2013 was 9,644, 864 of which 1, 533, 493 (15.9%) were born outside Sweden (7) (men: 748, 366 and women: 785, 127) (30). Currently, about one-fifth (20.7 %) of Sweden's population has a so called immigrant background (born outside Sweden or born in Sweden with one or both parents born outside of Sweden) (7).

2.1.1 Trends in immigration to Sweden

There are various reasons for immigration to a new country including labour, social, religious and political motivation. There has been a rising flow of immigration to Sweden since 1960 (Figure1 and figure 2). Foreign-born individuals comprised 11.3 % of the total Swedish population in 2000, up from 9.2 % in 1990, 7.5 % in 1980 and 4.0 % in 1960 (7). After the World War II, Sweden as an industrialized country actively began to recruit foreign labour, mainly from Finland, Germany, Greece, Italy, and the former Yugoslavia (29, 31). After the 1970s, immigrants have predominantly originated from non-Nordic countries, and were typically refugees seeking asylum on humanitarian grounds. Immigration waves to Sweden were from Uganda after 4 August 1972, from Chile following the revolution against President Salvador Allende in 1973, from Iraq and Iran in the 1980, and from the former Yugoslavia in the 1990 (31, 32). In the last two decades there has been a large inflow of immigrant to Sweden, both refugees and labour immigrants. Recently Sweden has offered resident permits to personns from the Middle East on humanitarian ground as demonstrated by its acceptance of refugees from the civil war in Syria. In 2013, the number of foreign-born residents from the Syrian Arab Republic was 41,748; this is more than twice the number of 19, 646 in 2009 (30).

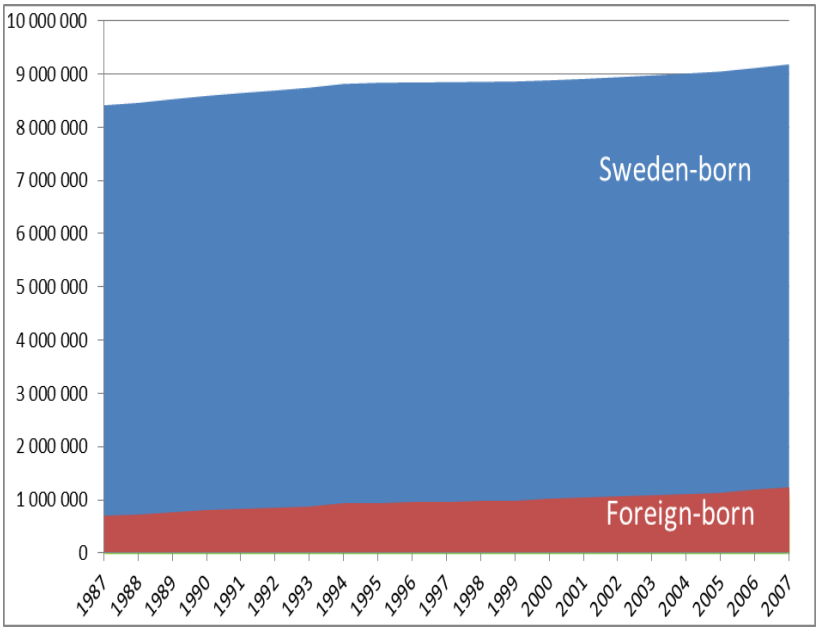


Figure 1: Swedish population in the years 1987-2007 by migration status (Sweden-born and foreign-born individuals) (Source: Statistics Sweden)

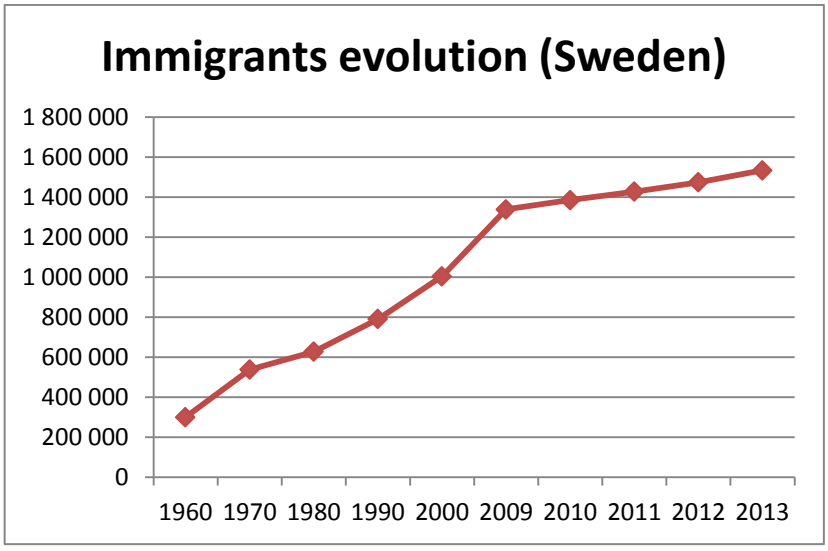


Figure 2: Foreign-born population in Sweden in the years 1960–2013 (Source: Statistics Sweden)

In 2013, the five leading countries of origin for immigrants to Sweden were Finland, Iraq, Poland, the former Yugoslavia and Iran (30) (Table 1).

Table 1: Number of foreign-born individuals in Sweden by country of birth in 2013

Country of birth	Number of foreign-born individuals	Percentage based on total population	Percentage based on immigrant population
Finland	161,129	1.67	10.5
Iraq	128,946	1.33	8.4
Poland	78,175	0.81	5.9
Former Yugoslavia	68,554	0.71	4.47
Iran	67,211	0.69	4.38
Bosnia and Herzegovina	56,804	0.58	3.70
Somalia	54,221	0.56	3.53
Germany	48,987	0.50	3.19
Turkey	45,676	0.47	2.97
Denmark	43,198	0.44	2.81

(Source: Statistics Sweden)

2.2 MIGRATION AND HEALTH

The multi-ethnic nature of the world population seems to be increasing due to globalization, travel, business, study and migration. An estimated 214 million international migrants and almost 0.75 billion people with internal migration are reported worldwide (33-35). Such a large degree of migration demands polices at both global and local levels to optimize resources for a better quality of life for all human beings. Recently, the effect of migration on health has become an important issue. At the beginning of the last century, the focus of health issues among immigrants was more on controlling communicable diseases in order to prevent the spread of the disease within the host population. Whereas nowadays the discussion on migration and health is more directed towards a human rights-based perspective i.e. “a healthy life for all”. Exploring the issue of migration and health is not only important because of the threat to society and to public health in the host country, but also in order to provide the same service to immigrants as to the host population (36, 37). The issue of migration and health has been described worldwide. In countries such as the United States and United

Kingdom with a long history of immigration, the disparities in health status among minorities have been widely reported (38, 39). Studies on health distribution between foreign-born individuals and the host population showed poorer health for Finnish people in Sweden (40, 41), and worse health outcomes among Irish and Scottish immigrants in England (42-44).

The findings of studies of the effect of immigration on health outcomes have been contradictory. Some studies have shown poorer health among immigrants compared to the host population. The largest immigrant group in Sweden is from Finland and an increased mortality risk for Finnish men and women has been found. In addition a higher risk of CHD mortality for women born in Finland and Eastern Europe has been reported (10, 11). However, others have shown opposite findings. Foreign-born individuals have been shown to have better health compared to the host population; for example lower mortality rates have been reported among black and Hispanic immigrants compared with US-counterparts, and foreign-born blacks have been shown to have the longest life-expectancy (45-48). The different health status among foreign-born groups compared to the host population may be due to differences in lifestyles, and in preventive or risky health behaviors (49). However there is a lack of comprehensive evidence to determine the true explanation for poorer or better health among the immigrant compared to the host population of a country. Many factors may explain this variation in health. It may depend on culture-based lifestyles, habits and norms; if these are unfavorable in the country of origin, immigrants will have a poorer risk profile than the host population (49). Furthermore, migration can be a stressful process, with increased anxiety, sleeping problems and stress. These factors may have a negative impact on psychological health, and may result in depression, anxiety and tension, and also post-traumatic stress disorder (50, 51). It is very difficult to clearly state whether migration is good or bad for individual health; this depends on the general state of the society and both population and individual health in the country of origin, as well as the general state of society and population health in host country. Also, immigrants health depends on immigrants' origin from high-income countries, and those or low-income countries, and on which individuals in these settings are more likely to emigrate (52). Is it the relatively sick and poor who emigrate, or the relatively rich and healthy who take their chances of an even better life somewhere else? However, emigration from countries of war is usually not voluntary and may be due to a forced choice which may have a negative impact on health among immigrants (53).

However, immigrants have also been shown to be healthier than persons of the same individual characteristics in the host country. The common explanation is the "healthy migrant effect" which has a positive selective effect on immigrant

health (46, 54, 55). In fact, there is an indication that immigrants also have better levels of health than the population in their country of origin, in particular young immigrants (55-57). It seems that the "healthy migrant effect" is stronger for immigrants coming from low income countries than from high income countries (58). This could reflect the fact that emigrants from low-income countries more often are those who already have resources and capabilities that can make emigration possible. On the other hand, persons with resources and capabilities in high-income countries might be satisfied with their life, whereas those without such resources and capabilities are more eager to emigrate. In general, this health advantage has been found to deteriorate (59, 60). Many factors can explain this advantage in health: a stronger social status and support network from the home country primarily provides a positive influence and exerts a protective effect on immigrants' health in the early years of immigration; but these factors are gradually lost as foreign-born individuals undergo a process of assimilation (61). Also, a less risky lifestyle with better diet and less tobacco smoking and a lower rate of excessive alcohol consumption may play a role. However other studies have found a health disadvantage among immigrants. The longer the foreign-born individual has lived in a host country the better was the health outcome. For example, in a study of Finnish immigrants in Sweden, the risk of MI was found to be higher compared to those born in Sweden. However, the relative risk of CHD decreased with duration of stay in Sweden. The mechanism of reducing risk of developing MI for men born in Finland in relation to duration of stay in Sweden is unknown (8). The authors of the study explained that the difference in relative risk of developing MI between Finland and Sweden is mainly due to environmental factors (8).

Migration itself is a complex and dynamic phenomenon with different related causes such as family ties, professional, economic and educational reasons and refugee. The psychobiological impact of forced migration, such as separation from friends and relatives, different language and culture, loss of contact with own ethnic group and loss of social status, may add to these mechanisms behind migration and health (38). Another issue related to migration and health is access to medical services. Some foreign-born individuals are unfamiliar with how to access services in the host country in an effective way and may face difficulties in contact with the healthcare services because of language barriers (62). These above are all recognized as underlying factors and have impact on inequities regarding migration and health.

2.3 SOCIOECONOMIC POSITION

Social inequalities in health are present worldwide as shown by the contemporary World Health Organization (WHO) report (63). In social epidemiology, different terminology has been used to describe social stratification in society, for example SEP, socioeconomic status, and social class. Indicators of SEP, for example occupation, education or income and wealth, or combinations thereof, have been used interchangeably (64). The following (i.e. ***Occupation-based, Wealth, income and education):*** are most common measures used in epidemiology.

Occupation-based has been commonly used as an indicator of SEP in some countries especially in Europe. For example the use of this variable is particularly popular in the United Kingdom (65), Sweden, Norway, Denmark and Finland. Occupation is strongly related to income; information about occupation may provide an indication of the individual level of income and reflect the social status associated with a variety of occupations.

Income another commonly used indicator of SEP, may indicate the ability of the individual to spend money on obtaining a good quality of life in terms of housing, place of work, food, lifestyle, sports and recreation. Income can also in some settings be an important means for the individual to access high-quality health care, especially in countries without universal health coverage. In the Nordic countries, information on income is registered with the national tax office and routinely collected from all individuals. Furthermore, it is possible to obtain information about income before and after paying tax. In surveys it might be difficult to collect accurate information from patients regarding income as it might be considered a sensitive issue. Also, in several settings, even in Sweden, the individual might have another source of income from the black market and in this case it is not possible to ascertain the real income of the individual.

Wealth is another indicator of SEP which reflects individual ownership regarding owning a house, savings, inheritance and others (65).

Another common variable used in social medicine to indicate individual SEP is level of ***education***. Nowadays, education is commonly used especially in the Nordic countries (17, 27, 66) and it can be accessed easily in national registers. Education can reflect the individual's likelihood of employment and is strongly related to income and social status. Education level can also mirror an individual's skill, general knowledge and health-related knowledge. The association between CHD and SEP is well known in both Sweden (67-74) and in other countries (75-80). Education has sometimes been considered to be more closely related than occupational status to heart disease (81, 82). The highest attained level of education has the advantage of being more constant as few

individuals continue schooling after age 35. Patients might be more willing to provide their education level rather than information about income and wealth. Furthermore, the association between education and disease may be less subject to reverse causality than income or occupation.

2.3.1 SEP and CHD

Inequalities in CHD incidence and mortality are complex, which may be due to multiple factors related to early childhood and adulthood life (83), behavioral and social risk factors (84) and access to care (85, 86). The association between low SEP and CHD may be explained by a higher prevalence of CHD risk factors (87-89) and CVD biomarkers (90, 91). However, a study have shown that the health disparities in different socioeconomic groups cannot be explained fully by the variations in risk factor levels (72). Furthermore, several studies have demonstrated that low SEP predicts CHD independent of traditional risk factors (79, 92-95). Fiscella and Tancredi explained the underlying pathways between SEP and CHD risk prediction (96). They believe that the association is likely to include biomedical (97), behavioral and psychosocial mediators (98). In addition, chronic psychosocial stress associated with low SEP induces atherosclerosis and CHD events (98). In addition individuals with a lower education level may confront more barriers to modifying their risk behaviors such as improving diet, quitting smoking, increasing physical activity and adhering to medications (27, 85) and cardiovascular interventions (86).

2.4 HEALTH EQUITY

Health equity and equality in access to healthcare are interrelated. The distinction between these two concepts has been discussed by others (99, 100). ***Health equity*** mainly refers to the justice, fairness and morality in providing healthcare especially for controllable aspects of health. Health inequity reflects dissimilarities in health that are avoidable, unjust, unfair and unnecessary (101). The disparities in health achievement reflect the ***health inequality***. The reason for the disparity may be because of biological, genetic and age differences between individuals. For example, young individuals in general have better health than those who are older, and women may develop cervical or endometrial cancer whereas men may have testicular or prostate cancer. There is no suggestion that this is unfair.

In some studies equality of access has been used as an practical definition of equity (102) with the term equity subdivided into horizontal equity – “a measure of equal treatment for those with equal need” – and vertical equity – “a measure of the extent to which individuals with unequal needs receive appropriately

different levels of care". The equity in health can be measured using the distribution of resources, health status (incidence and outcome of the disease) or access to and utilization of healthcare between groups with different ethnic, demographic or socioeconomic background.

The ethnic, socioeconomic and gender disparities in health and in access to healthcare are well documented (10, 13, 22-28, 103-107). In the USA, ethnic minorities receive lower quality of acute healthcare and less preventive care (107), and white children are more likely to receive routine healthcare than Hispanic children. The range of disparities varies among countries worldwide possibly due to differences in the availability of universal health coverage for all individuals in the country (105). In Sweden the coverage is universal. The Swedish Health and Medical Services Act of 1982 states that the health system must cover all legal residents. "Health and medical services are aimed at assuring the entire population of good health and of care on equal terms. Care shall be provided with due respect for the equal worth of all people and the dignity of the individual. Priority shall be given to those who are in the greatest need of health and medical care" (108).

The Swedish Health and Medical Services Act give county councils and municipalities substantial freedom with regard to organization of their health services.

It is important to note that Sweden has universal health coverage with a universally financed health care system with small out-of-pocket payment. In addition Sweden has systematic approach to minimize the disparities in health outcomes and to improve quality of care. For example in order to improve care coordination, a new waiting time guarantee for the patient, was introduced in 2005 and has been regulated by low since 2010 (108). This initiative, the 0–7–90–90 rule, requires: ''instant contact (zero delay) with the health system for advice; seeing a general practitioner within seven days; seeing a specialist within 90 days; and waiting no more than 90 days to receive treatment after being diagnosed''. Despite all efforts there are still disparities in health in Sweden (11, 46). Regardless of country of birth, there is inequality in obtaining adequate secondary prevention between educational groups (14, 17, 18, 66, 109, 110).

2.5 CORONARY HEART DISEASE (CHD)

CHD is a major component of the CVD. Health professionals frequently use the terms CHD and CVD interchangeably. CHD is also known as coronary artery disease (CAD), atherosclerotic heart disease**,** or ischemic heart disease (IHD). The five main manifestations of CHD are stable angina pectoris, unstable angina pectoris, myocardial infarction (MI), heart failure and sudden death. MI,

heart failure and sudden death., The incidence of MI in a population is often used as a proxy for measuring the CHD burden (111). CHD is a common term for the build-up of plaque along the internal walls of the coronary arteries, which leads to narrowing of the arteries and diminishes blood supply to the heart thus causing signs and symptoms of CVD including IHD and/or leading to MI.

2.5.1 Statistics and epidemiology of CHD

CHD remains the major cause of death worldwide (1-3) and in Sweden (5, 6). There has been a dramatic change in both the incidence of and mortality from MI in the past two decades. The number of MI-related deaths decreased from 18,000 in 1987 to 9000 in 2010. Between the years 2001 and 2003, the MI incidence was higher due to the introduction of new diagnostic criteria in 2001. Since 2004 there has been a decline in the incidence of and mortality due to MI. This decline has been dramatic; in 2011, the incidence was approximately 30% lower among both men and women compared to the year 2001 (5, 6).

There are several approaches to conducting epidemiological studies of global heart disease. Véronique L. Roger (111) has mentioned some examples of these established studies and surveillance such as the National Hospital Discharge Survey, community surveillance, Atherosclerosis Risk in Communities (ARIC), The Minnesota Heart Survey, Olmsted County Study, Framingham Heart Study, the Corpus Christi Heart Project, the WHO MONICA project and the Global Registry of Acute Coronary Events. Each of these studies used different methodology within well-defined populations and provided complementary information. Some were designed to analyze diverse ethnic groups such as ARIC and the Corpus Christi Heart Project whereas others had more limited ethnic diversity. Roger suggested the need for a national surveillance approach for epidemiological studies of CHD. This would provide better understanding of heart disease in the population. High-quality and complete nationwide surveillance can be achieved in Sweden because of the national health data registers.

Regional studies using appropriate designs to provide data on epidemiology of MI have been conducted in Sweden. The Stockholm Heart Epidemiology Program (SHEEP) is one of the largest population based case–control studies (14). SHEEP contains data about patient's characteristics and lifestyle factors as well as biomarkers. In addition, the unique Swedish registers provide excellent opportunities for population statistics and for conducting nationwide epidemiological studies on MI. A national record linkage between the National Patient Register and the Causes of Death Register was initiated in 1996 to

provide statistical information about acute MI (AMI) in Sweden (112). It is currently covering the period 1987–2011. This database provides data for monitoring MI, including information on incidence rates and case fatality, and can measure the true population burden of MI and how it may have changed over time. The possibility to link several sources of background information in Sweden makes it possible to conduct high-quality analytical research on the etiology of MI.

In summary, epidemiological studies provide data about the incidence and outcome of MI which is essential for determining the burden of MI in the population. Also, the analytical studies provide clues to the understanding of the etiology of MI.

2.5.2 Myocardial infarction (MI)

AMI is a condition caused by sudden deterioration of blood flow in the coronary blood vessel and thereby ischaemia within the heart muscle. The underlying cause is usually a rupture of an atherosclerotic plaque (plaque rupture). Atherosclerosis in the wall of coronary arteries is the gradual build-up of cholesterol and fibrous tissue in atherosclerotic plaques (113). Plaque rupture occurring in the coronary vasculature leads to AMI (114, 115). The phrase 'acute coronary syndromes' is also used in a clinical setting; this term includes unstable angina, non-ST-elevation MI (NSTEMI) and ST-elevation MI (STEMI), according to the appearance of the electrocardiogram (ECG), and sudden cardiac death (116, 117).

2.5.2.1 Definition of MI

The WHO has had a leading role in the formulation of standard criteria for the definition and diagnosis of MI and CHD (116, 118-120). In the early 1970s, the definition of MI was based on WHO European acute MI registry criteria and then further revised in 1979 by the International Society and Federation of Cardiology (116, 120). In 1979 the definition was primarily based on ECG changes (120, 121) and then shifted towards a biochemical and clinical approach in 2000 (121-123). In 1979, the diagnostic criteria were reported (120). In 2000, collaboration between the European Society of Cardiology (ESC) and American College of Cardiology (ACC) lead to a new definition of MI. The redefinition of MI was important in the cardiology field, coinciding with the introduction of a new cardiac biomarker, troponin, for the diagnosis of MI (122). The ESC and ACC consensus document for the redefinition of MI was published in September 2000, including a summary of the diagnostic criteria (122).

The second joint document for defining MI was published in 2007 when the ESC and ACC were joined by the American Heart Association (AHA) and the World Heart Federation (WHF). In this consensus document, the use of troponin as a primary biomarker was recommended (121, 124, 125). There was debate about the 2007 universal definition of MI. WHO claimed that the definition was only suitable for countries with high-quality resources and not for resource-poor countries, i.e. that it was only appropriate for Europe and North America (121).

The third universal definition of MI in 2012 was a consensus document between the ESC, American College of Cardiology Foundation (ACCF), AHA and WHF and included members from 52 countries including China and Russia. The sections of the document concerning detection of MI using ECG and imaging techniques were revised in 2007 document. The consensus document included both updated definitions and a revised classification of MI which have significant clinical, epidemiological and research implications (126).

2.5.2.2 Clinical classification of MI

In 2007, for the first time in the history of MI definition, the global task force classified MI into five different types. "The 2007 document was more widely accepted by clinicians" (121). In Sweden the 2007 criteria for classification of MI (125) were used until 2012. The 2007 criteria were as follow:

*"*Type 1 Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection.

Type 2 Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension.

Type 3 Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischaemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

Type 4a Myocardial infarction associated with PCI.

Type 4b Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy.

Type 5 Myocardial infarction associated with CABG*".*

The modified classification of MI was published in October 2012 by the Global myocardial Infarction Task Force.2, (126).

2.5.2.3 Recurrent MI

The difference between recurrent MI and reinfarction is sometimes unclear. Recurrent MI refers to when a new MI occurs after day 28 following a first MI. However, if characteristic features of MI occur within the first 28 days after an incident MI, this is not considered as a new MI event for the public health and epidemiological purposes. This instead referred to as a reinfarction, i.e. when a "new" MI occurs within 28 days of a first incident MI or recurrent MI (116, 126). The criteria for definition of reinfarcton have been reported (126).

2.5.3 Management of MI

Management of this disease includes diagnosis (history, clinical examination and investigation), treatment (acute and long-term medical therapy) and secondary prevention. MI is an acute emergency condition; it is critical to rapidly diagnose MI to be able to provide correct treatment in order to save the life of the patient. Therapy varies according to the type of MI (STEMI or NSTEMI), but the first main goal is the same: to restore perfusion and prevent and minimize ischaemia by medical therapy/and or interventional and surgical measures such as percutaneous coronary intervention (PCI) or CABG. The next step is long-term therapy and the secondary prevention of MI in order to limit complications and further recurrence to decrease morbidity and mortality (127, 128).

2.5.3.1 Treatment and long term Pharmacotherapy

Drug therapy is a core component of the management of CHD in both the acute phase and in long-term treatment. The choice of a medical treatment depends on the specific situation and varies from one individual to another. Pharmacotherapy and secondary prevention are necessary and should be accessible for all patients (129). The 2002 ACCF/AHA guidelines are useful for the long-term medical therapy and secondary prevention of CHD (130). The guidelines recommend use of the 'ABCDE concept': aspirin, anti-anginals and angiotensin-converting enzyme (ACE) inhibitors (A); beta-blockers and blood pressure (B); cholesterol and cigarettes (C); diet and diabetes (D); and education and exercise (E).

There are drugs essential for primary and secondary care for MI (128). All patients who have had a history of MI and those who have undergone myocardial revascularization should be offered treatment with a combination of medication. Several drugs (antiplatelet agents, beta-blockers, ACE-inhibitors, and statins) are well-known to improve prognosis of MI patients (131-138).

- **Aspirin:** reduces cardiovascular mortality and morbidity. Aspirin has a protective effect in most patients with increased risk of vascular occlusive events, including those with an AMI, previous MI, stable or unstable angina and ischaemic stroke (132, 133, 139)
- **Beta-blockers**: administered long terms to patients after MI have been shown to improve survival and reduce total mortality and cardiovascular morbidity (132, 138, 139).
- **ACE inhibitors**: are effective in reducing mortality, the risk of MI and in certain patients the risk of developing heart failure (132, 135, 136, 140-142).
- **Statins**: are essential for the prevention of cardiovascular events. These agents reduce total mortality and cardiovascular morbidity (132, 134, 139, 143).

2.5.4 Coronary artery bypass grafting (CABG)

In late 1960s, CABG was introduced to treat the symptoms of obstructive CHD (144). The operation is documented as an effective treatment in a high proportion of patients with CHD (145-147). During the last decade a decline in the number of CABG procedures has been observed due to the advent and expansion of percutaneous coronary interventions (PCI) (148-150). In Sweden, the number of heart operations has continues to decrease slightly in comparison with the preceding year. In 2013, a total of 5, 760 open heart procedures were reported in Sweden. Fewer isolated CABG procedures were performed, 2, 575 operations compared with 2, 705 during 2012 (5).

2.5.5 Risk factors of CHD

There are several risk factors for heart disease; the most well-known non-modifiable and modifiable risk factors are age, sex, family history and genetics, as well as dyslipidemia, smoking, hypertension, glucose intolerance, central obesity, and psychosocial factors (151-153).

Non-modifiable risk factors: The risk of emerging CHD increases with age (154), and men develop heart attacks at ages >45 years i.e. younger than women who develop the disease >55 years, also mortality rates tend to be higher for men

(155). It has been found that, on average, women experience a first MI 9 years later than men (156). A family history of early-onset CHD in first a degree relative (father or brother with CHD at age 55, and mother and sister at age 65), has been considered a risk factor for CHD (157). Ethnicity as a non- modifiable factor has also been investigated; previous studies showed ethnic differences in the development of CHD and atherosclerosis (158, 159).

Modifiable risk factors: The results of many studies have suggested that smoking, dyslipidaemia and blood pressure are the most significant factors with regard to IHD incidence and mortality (160-162). Furthermore controlling for these risk factors by continued management of blood pressure, dyslipidemia, diabetes, and life style changes (exercise, healthy diet and cessation of smoking) (153, 163) has a considerable impact on disease prevention and reduction of premature death (89, 164).

Studies have shown a strong relationship between cigarette smoking and heart disease. In 2000, it was estimated that 800,000 deaths due to CHD could be attributed to smoking (165). Cessation of smoking leads to a reduced recurrence rate within 1 year among patients who have had an MI and decreases the risk of sudden cardiac death among patients with CHD (166). Termination of smoking leads to reduction of recurrence rate within 1 year among patients who have had MI and decreases the risk of sudden cardiac death among patients with CHD (166, 167).

An abnormal lipid profile is the main contributor to CVD globally. The findings of the INTERHEART study demonstrated that tobacco was the second main risk factor after lipid profile. Other common risk factors are hypertension, diabetes, abdominal obesity and psychosocial factors (89). Some of these risk factors are correlated to each other. Subsequent studies confirmed that dyslipidemia is a significant risk factor (160-162) and further established that raised triglyceride levels increase CVD risk. Furthermore, reduction of low-density lipoprotein (LDL) cholesterol is important in both primary and secondary prevention of CHD. These findings have been confirmed in many studies (168, 169). Recent clinical trials showed that lowering LDL cholesterol by intensive lipid-lowering therapy reduces the rate of MI and mortality (170). The reduction in cholesterol was the most important factor in the overall decline in CHD mortality in Finland between the 1970s and early 1990s (171).

Abnormal blood pressure has an impact on the risk of CVD, increasing the risk 2-fold compared with healthy individuals (172). Diabetic patients are more prone (2- to 8-fold increased likelihood) to develop CVD in the future (173, 174). Furthermore CVD is an important cause of morbidity and mortality in diabetic patients (175, 176). Obesity is the main risk factor for type 2 diabetes, but

unhealthy diet and physical inactivity have been shown to be independent risk factors for diabetes (177).

Furthermore other life style and psychosocial factors are associated with risk of MI and have an important role in increasing CVD risk at all ages and in both sexes (89). Depression, life stressors, anxiety, anger and lack of social support are factors that have been associated with CVD (178-180). Such factors have been linked to the increased risk of sudden death, and recurrent MI. Anxiety and chronic stress have also been linked to negative behaviours such as low physical activity and poor diet and have an impact on CVD outcomes (178, 179).

Other diseases are linked to CVD including chronic inflammatory disorders such as systemic lupus erythematosus and rheumatoid arthritis (181, 182). Furthermore CHD is due to a complex interaction between environmental factors and numerous genetic variants. The first known genetic variant for CHD was discovered by a genome-wide association study of chromosome 9p21.3. The increased risk for MI detected with single-nucleotide polymorphisms from the 9p21.3 (183-185).

3 AIMS

3.1 OVERARCHING AIM

The overarching aim of this thesis was to increase knowledge of the effect of country of birth on management, prognosis, and access to health care services in patients with CHD in Sweden.

3.2 SPECIFIC OBJECTIVES

- To study the incidence and time trends of MI in relation to country of birth, SEP, gender and age (Study I).
- To investigate mortality after 28 days following an incident MI in relation to country of birth, SEP, gender and age (Study I).
- To investigate cardiovascular drug use after first MI in relation to country of birth, SEP, gender, age and drugs used before MI (Study II).
- To evaluate the risk and trend of recurrent MI in Sweden in relation to country of birth, SEP, gender and age (Study III).
- To determine the effect of duration of residence and age at immigration on recurrence of MI (Study III).
- To study mortality after CABG in relation to country of birth, SEP, gender and age (Study IV).

4 MATERIALS AND METHODS

4.1 SWEDISH PERSONAL IDENTITY NUMBER

The Swedish personal identity number (PIN) is vital in many aspects of Swedish society and serves as a unique identifier in Swedish healthcare and national registers. The PIN was established in 1947. From 1967 the 10-digit PIN has consisted of the date of birth, a three-digit birth number and a single check digit. The three-digit number can take any value between 001 and 999, and is odd for men and even for women (i.e. is sex specific) (186). The PIN was principally a useful means of identifying individuals. Nowadays it is widely used in public administration, vital statistics, for research purposes, and as the key variable for linkage and matching between different national demographic registers and health data registers, quality registers in healthcare and biobank (187). A person who is born in Sweden or who moves to the country and intends to stay for at least 1 year will receive a PIN, and is thus entered in the Total Population Register. The PIN is unique to each individual, and preserved for life. Individuals remain registered in Sweden until the day they move abroad or die (188).

4.2 LINKAGE TO SWEDISH NATIONAL REGISTERS

Two main authorities handle register linkage for health research purposes: Statistics Sweden and the National Board of Health and Welfare (186). The data used in our study were collected by linkage to several national registers through the PIN. The data used are based on the newly established Migration and Health Cohort (189) specifically designed to address health status among immigrants in Sweden. This database serves as a link between more than 15 national registers including cancer, CVD, diabetes, injury and psychiatric disorders among foreign-born persons and their descendants.

4.3 TOTAL POPULATION REGISTER (TPR)

Sweden is one of the countries with oldest population statistics, with continuous information dating back to the 18th century. In 1968, the national civil registration was computerized and the Total Population Register (TPR) was established. From 1969, the TPR has been the base register for authorized Population Statistics in Sweden (190). The TPR comprises most of the data found in the civil registration, and covers the entire population resident in Sweden.

The Swedish Tax Agency is in charge of the population register (188). The following information included in the register (188):

- Name
- Address
- Personal identity number and co-ordination number
- Place of birth (country, county, and parish)
- Place of residence (region and address)
- Citizenship
- Civil status (never married, married, partner, divorced, widow/widower)
- Spouse, children, parents, legal guardians and adoption
- Moves to and from Sweden
- Addresses abroad
- Death and burial site.
- Sex
- Age
- Immigration (date, country, ground for settlement)
- Relations (married couples, child – parent)

Dates are also added to the register, e.g. wedding date (188). The quality of the TPR is generally very high. However, it is suspected that there may be an under-reporting of information, foremost of emigration from the country (i.e. persons moving out of Sweden without notifying the authorities), although the exact magnitude of this is unknown (191, 192) . To be registered as an immigrant in Sweden one must intend to stay in Sweden for at least 1 year. Likewise, registration as an emigrant requires that the person emigrating must intend to reside abroad for at least 1 year.

4.4 CAUSES OF DEATH REGISTER

The Causes of Death Register is managed by the National Board of Health and Welfare and comprises data from 1961 updated annually. There is also a historical mortality register for the years 1952-1960 (193). International Classification of Diseases (ICD) (ICD-6) was adopted by the World Health Assembly in 1948 and introduced in Sweden in 1951. Newer revisions of the ICD were introduced in 1958 (seventh revision), 1969 (eighth revision), 1987 (ninth revision) and 1997 (tenth revision) (194, 195). The Causes of Death Register covers all deaths among individuals who were registered in Sweden in the year they died, whether the death occurred inside or outside the country. The register does not include stillbirths, or persons who died during a temporary stay

in Sweden or asylum seekers who have not yet received a residence permit. Swedish emigrants, who are no longer registered in Sweden, are also excluded (193). When the death of a Swedish citizen occurs inside Sweden, a physician will submit a death certificate to the Swedish Tax Agency. If the death occurs abroad, the Swedish embassy or consulate in that country shall inform the Swedish Tax Agency as soon as they are aware of the death (188). The register contains:

- Personal identity number
- Place of death
- Underlying and contributing cause of death
- Date of death
- Sex, marital status and age

The quality of death registers can be influenced by the age of the deceased individual. An elderly person may have a more complicated cause of death compared to a young person, and it might be difficult for the physician to write a precise death certificate in some circumstances (191). Autopsies also provide good information regarding cause of death however, the number of autopsies have gradually decreased from 50 % during the 1970 to 14% in recent years (191, 196). The National Board of Health and Welfare aims to count all deaths among Swedish residents, whether or not the death was in a Swedish citizen and whether the death occurred inside Sweden or abroad. However, in 1.9% of all deaths reported to the TPR, the national Board of Health and Welfare was not able to obtain a death certificate. The register has a wide range of applications for Swedish statistics and for medical research.

4.5 NATIONAL PATIENT REGISTER

At the beginning of 1960 the National Patient Register (NPR) covered six out of the 26 county councils in Sweden. The NPR was started in 1964 and became nationwide in 1987 (including all inpatient care in Sweden). From 2001, it has recorded somatic and psychiatric specialized outpatient visits from both private and public caregivers including day surgery. From the period 1964–2006, 50 million discharges were recorded (197). The register includes patients' data, geographical data, admission and discharge dates, and data on the hospital or clinic in which a patient was treated, as well as some data on type of admission, diagnoses and procedures. The quality of the NPR is very high. Regular quality control of the PIN, hospital, main diagnoses and secondary diagnoses, and admission and discharge dates is conducted.

The validity of the Swedish NPR is high for many variables. Of all admissions during the period 1987–2011, only 1.1% of primary diagnoses were missing from this register. For somatic care, the proportion of missing data is below 1%. Data from this register are useful for large-scale population-based research. For some diagnoses and for certain research areas the use of other health registers is recommended. For instance, the Swedish Cancer Register is more appropriate for studies on cancer incidence (198). Of note, there is no national register for primary healthcare in Sweden.

4.6 ACUTE MYOCARDIAL INFARCTION DATABASE

The nationwide Acute Myocardial Infarctions (AMI) database was introduced in 1996 by a record linkage between the NPR and the Causes of Death Register. It comprises all AMIs reported to either register and is updated annually by the National Board of Health and Welfare. It covers the whole country from 1987. In most cases the MI patient can be identified in a population because MI is an emergency condition and patients either die or are treated in hospital. The main variables in the AMI database include PIN, sex, age at diagnosis of MI, birth date and dates of admission, discharge and incidence of MI. The quality of the database has been evaluated and found to be very high (199). There is no information on those who have been admitted to hospital from abroad due to an MI, as the NPR is an administrative register only covering care in Sweden (200).

4.7 THE SWEDISH HEART SURGERY REGISTER

In addition to the national health data registers Sweden also has several national quality registers. These registers are not covered by the same regulations as the national health data register. Hence, reporting from the health care providers to these registers is voluntarily, and the patients can also deny to be reported in these registers. This is in sharp contrast to the national health register where the health care providers must report all in-patient care and all specialized out-patient care, and the patients cannot deny recording.

Since the establishment of Swedish Heart Surgery in 1992, all open-heart surgery performed in Sweden is reported to this national quality register that has complete coverage. It contains data about more than 100 000 heart operation. All heart operations including coronary artery bypass graft (CABG) are included yearly with demographic data, information on type of operation, certain postoperative complications and risk factors according to Euro SCORE (European System for Cardiac Operative Risk Evaluation). Diseases are coded according to present ICD-codes and surgical procedures according to the Swedish version of Nordic Medico-Statistical Committee (NOMESCO) (201).

Open heart surgery procedures including CABG were more than 7 000 during 1992. The maximum was in 1994 with 9 512 operations. From 2002 to 2008, cardiac surgery decreased by 20%. The number of isolated CABG procedure decreased by 44% during the same period.

The register is a reliable source of data for heart surgery. Information is reported to the register on-line or on a designated report card including up to 101 items (5, 202). In January 2010, the web-system was established in Sweden for patient with admitted to hospital because of acute coronary syndrome.

4.8 PRESCRIBED DRUG REGISTER

In Sweden, a national register of dispensed drugs was established in July 2005. It covers the whole Swedish population with valuable data for all dispensed drugs. The Swedish Prescribed Drug Register represents one of the largest population based pharmacoepidemiological records in the world and can offer new possibilities for local and international pharmacoepidemiological research. The potential for research by record linkage to other health registers is huge. Data gathering is managed by the National Corporation of Swedish Pharmacies and the register is regulated under Swedish legislation (27, 203). All drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system (204).

The register contains the following data: dispensed item – substance, brand name, formulation and package; dispensed amount – dosage and expenditure; age, sex and unique identifier (PIN); place of residence – county, municipality and parish; date of prescribing and dispensing; practice (primary healthcare center or hospital clinic) that has issued the prescription, identified by a code; and the prescriber's profession – e.g. general practitioner, internal medicine specialist, psychiatrist or paediatrician (203).

The indication for medication is not available and the register only covers dispensed drugs i.e. information about prescribed drugs by the physician which are not collected by the patient are not recorded. The register does not contain records on treatments used in hospitals, in nursing homes and is not complete with regard to information about vaccination. Over-the-counter drugs (OTC) are not recorded.

4.9 THE SWEDISH NATIONAL POPULATION AND HOUSING CENSUS

The Swedish National Population and Housing Census contain information on the total population of Sweden between 1960 and 1990. The information is updated every 5 years from a questionnaire delivered by post to

every household in Sweden. The census includes demographic and socioeconomic data as well as information on housing and employment for each household member resident in Sweden.

4.10 LISA

Longitudinal Integration database for health insurance and labor market studies (LISA) is a database linked to information from several registers. LISA was established in 1990 and the information is updated annually. It contains data incorporated from the labour market and from educational and social sectors, and includes demographic, occupational and socioeconomic variables such as individual, family and capital income, education and marital status.
The benefit of LISA is that it permits follow-up over time of an individual's status. LISA is a compilation of many other registers with more detailed information. In addition, it comprises thorough information on sickness leave, parental leave, unemployment and social insurance (205).

4.11 ETHICS STATEMENT

All the studies included in this thesis were approved by the Regional Board of the Ethical Committee at Stockholm. (Dnr: 2005/726-31, 2008/945-32 and 2009/587-32). Ethical vetting is always required when using register data for research in Sweden. The ethical review board provides the researcher with the anonymized data. The real personal identity number (PIN) is replaced by a serial number by the National Board of Health and Welfare or statistics Sweden to ensure the confidentiality. In the present project the linkage has been completed via 10-digit PIN. The personal integrity was not violated. By Swedish law data recording to national health data registers, like the NPR, do not require consent from the patients, nor from the health care providers. It is obligatory to report to these registers, and the patients cannot decline registration. One argument is that the possibility to work with this anonymized data for research purposes is of benefit to society and the benefit overrides the potential harm. The quality health care registers, like the Heart Surgery Register, are voluntary and the patients must be informed about the register, but they do not need to give written or oral consent to be recorded. However, patients can at any time decide to not allow registration in these quality health care registers. The researcher has to protect the personal integrity and follow the ethical rules regarding security of the data storage and agree to never back track to the identity of the individual (186). We present data for immigrants from specific countries; this may be regarded as a kind of stigmatization for people from these countries. However, we feel it is of

great importance to highlight these country specific data in order to improve public policy, health and health care for these populations.

4.12 METHODS

The data sources for all four studies are derived from Migration and Health Cohort (189) (Table 2). The two main groups in all studies were Sweden born individuals (those born in Sweden) as a reference group and foreign-born individuals (those born outside Sweden) as the exposed group. The analyses were stratified by sex.

4.12.1 Study period

Study I

Incidence of MI: Individuals were followed from 1 January 1987, first immigration date for foreign-born or the first date at age 35 years old, whichever occurred last, until the date of diagnosis of an acute MI, first emigration date, death, first date at age 90 years old, or end of follow-up (31December 2008), whichever occurred first.

Mortality after MI (Case fatality): Non-fatal MI cases were followed from the date of diagnosis until the date of death due to MI either as an underlying or contributory cause, death due to other causes, first emigration date, first date at age 90 years, or end of follow-up (31 December 2008), whichever occurred first.

Case fatality was mentioned because we followed MI cases.

Study II The study population consisted of all incident cases with a first AMI during the study period (1 January 2006 to 31 December 2007). The study was restricted to those patients who survived at least 6 months after AMI.

Study III Patients were followed from the date of first MI until the date of second MI, date of first emigration, date of death, or end of follow up (31 December 2007), whichever came first.

Study IV Patients were followed from the date of CABG until the date of death from any cause, date of emigration or end of follow-up (31 December 2007), whichever came first.

4.12.2 Exposure variables

The main exposure variable in this thesis was Migration status (country of birth) (Table 2) and to more extent country of birth. For all four Studies, we classified foreign-born We classified foreign-born individuals according to six continents, which were subdivided into 19 world regions, as defined by the United Nations Population Division (206) (Studies I, II, III and IV):

Africa (Eastern, Central, Northern, Southern, and Western Africa),

Asia (Eastern, South-Central, South-Eastern, and Western Asia),

Europe (Eastern, Northern, Southern, and Western Europe),

Latin America (Caribbean, Central America, and South America),

North America (USA and Canada) and Oceania (Australia/, New Zealand, Melanesia, and Micronesia, Polynesia),

For Study II, we included the following categorization:

Sweden (individuals born in Sweden);

Nordic (individuals born in Finland, Denmark, Norway or Iceland);

EU-countries and Switzerland (individuals born in EU);

Other-European countries (individuals born in Europe but outside the EU); Outside-EU (individuals born outside Europe)

In addition, we dichotomized patients as born in Sweden or not. We reported information for all continents and regions, as well as for all individual countries with five or more outcome.

We also studied the association between SEP (in all four studies) and sex in (Studies I, III, IV) and outcome when it was applicable in our studies. We used the highest attained level of education as an indicator for SEP. We divided levels of education into four categories: 0–9 years (compulsory school education), 10–12 years (upper secondary), more than 12 years (post-secondary), and unknown. Also, age at immigration (younger than 14, 15–39, 40–64, and 65 years +) and duration of residence in Sweden (less than 14 years, 15–34, and 35 years +) were investigated in Study III.

4.12.3 Outcome variables

Different end points related to CHD were the outcomes of interest: First, MI (study I), death due to MI as an underlying cause or contributing cause of death, and death due to any cause (Study I), odds of cardiovascular drug use (Study II), fatal and non-fatal second MI (Study III) and death due to any cause (Study IV). Drugs prescribed after MI included in Study II were: acetyl salicylic acid (ASA) and clopidogrel (ATC codes: B01-AC04, B01AC06; defined as C),

beta-blockers (C07; defined as B), lipid-lowering drugs (C10; defined as L), ACE inhibitors (C09; defined as A) and vasodilators nitrates (C01; defined as N). Drugs were grouped into five categories: *i)* recommended drugs or adequate combinations of recommended drugs (LBAC, BAC or BC); *ii)* Other, other combinations of recommended than (LBAC), (BAC) or (BC)); and *iii)* None of the recommended drugs. According to Swedish guidelines on drug use in CVD, drugs are ranked on a scale from 1 to 10. The medication considered to be of highest priority is assigned rank order 1. The first three combinations (LBAC, BAC and BC), in our categorization of drug use after MI are ranked first, second and third, respectively, according to the guidelines. Only prescriptions filled within 180 days after MI were studied.

4.12.4 Explanatory variables

Study I: age, education, comorbidities, and calendar years of follow-up. Age was divided into eleven groups in 5-year intervals (35–39, 40–44… 85–89 years). We divided study period into four time periods (1987–1990, 1991–1995, 1996–2000 and 2001–2008). Comorbidities (diabetes, hypertension and hyperlipidaemia) were considered in the analysis as binary variable (yes/no). In all four studies highest attained level of education was used as a proxy for SEP and we divided levels of education into four categories as described above.

Study II: age, sex, education, diabetes and marital status. Age at diagnosis of MI was divided into four groups (younger than 60, 60–69, 70–79 and 80 years and older). Diabetes was considered in the analysis as a binary variable (yes/no).

With regard to marital status**,** we have classified married and register partners as married and all others as unmarried.

Study III: age, calendar year of follow up of first MI, and educational level. Age was divided into eight groups (30–49, 50–54, 55–59, 60–64 . . . , and 80–84 years). We divided study period into four intervals: 1987–1990, 1991–1995, 1996–2000, and 2001–2007.

Study IV: age, calendar year of surgery, waiting time for surgery, diabetes mellitus and education. Age at surgery was divided into five groups (younger than 50, 50–59, 60–69, 70–79 and 80 years and older). The year of surgery was divided into three groups (1995–1998, 1999–2002 and 2003–2007). Waiting time for surgery was categorized into five groups (as an emergency within 24 hours, 1–6 days, 7–30 days, 31–90 days and longer than 90 days). Diabetes was considered in the analysis as a binary variable (yes/no).

Table 2. An overview of the four studies

	Study I	Study II	Study III	Study IV
Aim	To study the incidence and the time trends of MI and to investigate mortality after 28 days following an incident MI in relation to country of birth, SEP, gender and age	To investigate cardiovascular drug use after first MI in relation to country of birth, SEP, gender, age, and drugs used before MI	To evaluate the risk and trend of recurrent MI in Sweden in relation to country of birth, SEP, gender, and age. To determine the effect of duration of residence and age at immigration on recurrence of MI	To study mortality after CABG in relation to country of birth, SEP, gender and age
Study population	Swedish Total population (n=3, 426,243 men and 3, 326,412 women) and all non-fatal first MI patients (n=224, 498 men and 141, 587 women, of which 35, 066 were foreign-born (21, 431 men and 13, 635 women)) (1987-2008)	All non-fatal first MI patients including n= 37, 570 (of whom 4, 782 (12.7 %) were foreign-born, who survived at least 180 days after MI) (2006-2008)	All non-fatal first MI patients including n=469, 261 (Sweden-born: 300, 715 men and 168, 546 women) and 49, 242 foreign-born: 31, 033 men and 18, 209 women). (1987-2007)	All individuals who underwent a first isolated CABG including n= 72, 333 (Sweden-born: 48, 301 men and 14, 855 women) and foreign-born: 6, 685 men and 2, 492 women). (1995-2007)
Design	Cohort study	Cohort study	Cohort study	Cohort study
Data sources	Migration and health cohort including: National patient Register, Causes of death register, Total Population register, Swedish Population and Housing Census and longitudinal integration database for health insurance and labour market	Migration and health cohort including: National patient Register and Causes of death register (Myocardial infarction Database), Prescribed Drug register, Total Population register, Swedish Population and Housing Census and longitudinal integration database for health insurance and labour market	Migration and health cohort including: National patient Register and Causes of death register (Myocardial infarction Database), Total Population register, Swedish Population and Housing Census and longitudinal integration database for health insurance and labour market	Migration and health cohort including: The Swedish Heart Surgery Registry, Swedish Coronary Angiography and Angioplasty Registry (SCAAR) and the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA), The Register of the Total Population, Causes of Death Register, and the Swedish Population and Housing Census and the longitudinal integration database for health insurance and labor market studies
Main exposures	Country of birth and SEP	Country of birth and SEP	Country of birth and SEP	Country of birth and SEP
Main outcomes	First MI incidence and mortality after MI	Filled prescriptions after MI	Recurrent MI	Mortality after CABG
Statistical analysis	Poisson regression and Cox proportional hazard regression	Logistic regression	Cox proportional hazard regression	Cox proportional hazard regression

5 STATISTICAL ANALYSIS

5.1 COX PROPORTIONAL HAZARD REGRESSION

We used multivariate Cox proportional hazard regression in Studies I, III and IV to model risk of first MI case fatality, second MI and mortality after CABG, respectively. The most commonly applied model in medical time-to-event studies is the Cox proportional hazards model, i.e. a multiplicative association between the underlying hazard functions and a log–linear function of the covariates. The model assumes proportionality of hazards; it is assumed that the hazards for patient subgroups are proportional over the follow-up period (the two hazard curves are thus assumed to be parallel on a log scale). Hazard ratios (HRs) with 95% confidence interval (CIs) were used to compare different groups. The assumptions of Cox regression were examined using a martingale-based graphical and numerical approach.

5.2 LOGISTIC REGRESSION

Logistic regression is a form of regression modelling that is useful to predict a binary response variable. The probability of success is modelled as a function of a set of covariates, x1… xq. The odds ratio (OR) with 95% CI was calculated to compare the odds of drug use after MI among different groups.

5.3 POISSON REGRESSION

We used Poisson regression to calculate incidence rate ratios (IRRs) of first MI with 95% CI (Study I) in an adjusted analysis. Poisson regression is a generalized linear model in which the response variable is assumed to follow the Poisson distribution.

5.4 JOINTPOINT REGRESSION

To analyse the time trends of first MI we used the Jointpoint regression model (Study I). The processes in the analysis using Jointpoint regression involve fitting a series of joined straight lines on a log scale to the trend of incidence rate data for age-standardized rates. The change in trend in each point can be identified when it is statistically significant. The program starts with the lowest number of jointpoints and checks whether more jointpoints are statistically significant and must be added to the model. The annual percentage change (APC) can be estimated by this method to denote the trend and to test statistical significance. The null hypothesis in the analysis using this method is that there

is no alteration in the trend of incidence rates, i.e. neither increasing nor decreasing (191).

6 RESULTS

6.1 STUDY I

Incidence and case fatality after day 28 of first time myocardial infarction in Sweden 1987-2008

Aim:

To study the incidence and time trends of MI in relation to country of birth, SEP, gender and age

To investigate mortality after 28 days following an incident MI in relation to country of birth, SEP, gender and age

Incidence of MI

During the study period (1987–2008) we observed 571,476 cases of first-time MI (344,349 men and 227,127 women), of which 49,735 were in foreign-born individuals (29,655 men and 20,080 women). In both sexes and regardless of country of birth, a decreasing trend in first-time MI incidence was observed. The trend was, however, less pronounced among women and those born outside Sweden. Men had a higher incidence of MI than women (IRR 2.09, 95% CI 2.08–2.11). The incidence of first-time MI decreased with increasing level of education in both sexes and regardless of country of birth. A higher incidence was found among individuals with less than 9 years of education compared to those with more than 12 years of education. The incidence was 50–85% higher in the group with the least education irrespective of sex and birth country. The increased risk by education level remained stronger among women but was more pronounced in Sweden-born (IRR 1.85, 95% CI 1.81–1.89) than foreign-born individuals (IRR 1.77, 95% CI 1.67–1.87). Regardless of country of birth, comorbidities were associated with increased risk of first-time MI. However, the association between history of hypertension or diabetes and first-time MI was more pronounced among foreign-born than Sweden-born individuals of both sexes (see Paper I). Age-standardized rates were higher in men than women as well as in stratified analysis by country of birth. The trend based on jointpoint regression analyses during the study period, between 1987 and 2008, was more prominent among Sweden-born (men: APC -2.1, $p<0.0001$ and women: APC -1.0, $p<0.0001$) than foreign-born individuals (men: APC -1.2, $p<0.0001$ and women: APC -0.4, $p=0.05$) (see Paper I). However, temporary increases in age-standardized rates for both sexes were found around the year 2001 (see Paper I). At the country level and compared with Sweden-born individuals, men and women from Western Asia, Europe, Northern and Eastern Europe showed high

incidence of first-time MI. Men born in Southern and Western Asia had a 50% (95% CI 40–60%) higher risk than men born in Sweden. By contrast, men and women from Eastern Africa, South-Eastern Asia, Western Europe and Latin America showed lower first-time MI incidence. We observed the highest 3- and 4-fold significant increased risk among men born in Bangladesh and Armenia, respectively, after multivariable adjustment. The lowest MI incidence rate decreases of about 50% and 70% were found among men born in Japan and Bolivia, respectively. The highest incidences were found among women born in Pakistan and Afghanistan (2-fold increase) and in Serbia (4-fold increase) compared to Sweden-born women. The lowest incidences were found in women born in Morocco, Somalia, Japan and China (decreased by 40–60% compared to Sweden-born women).

Mortality after day 28

During the study (1987–2008) there were 37,416 and 25,122 cases of MI-specific deaths among men and women, respectively. A downward trend in mortality risk was found throughout this period. Regardless of sex and country of birth, MI patients with a low level of education had around 50% statistically significantly worse prognosis compared with those with more than 12 years of education. We observed a 15% higher case fatality after day 28 among men than women (HR 1.15, 95% CI 1.13–1.17). We found the same association between high levels of education and estimated case fatality after day 28 due to IHD, and to a lesser degree due to any cause. We also found a negative association between case fatality and diabetes. In addition, an improvement was detected regarding mortality after MI during the study period.

6.2 STUDY II

Recommended drug use after acute myocardial infarction by Migration status and educational level

Aim:

To investigate cardiovascular drug use after first MI in relation to country of birth, SEP, gender, age and drugs used before MI

The study comprised 4782 foreign-born and 32,788 Sweden-born patients. There was no apparent significant difference in drug use after MI between foreign-born and Sweden-born patients after taking into consideration drugs used prior to MI and adjustment for age, sex, marital status and education. Among those who did not take any cardiovascular drugs before MI, there were no differences in drug use after MI by migration status (OR 1.00, 95% CI 0.89–1.12). Among those who took some but not all recommended cardiovascular drugs before MI,

foreign-born cases had a slightly lower but non-significant use of recommended drugs in the adjusted model (OR 0.92, 95% CI 0.83–1.03). Although not statistically significant, but there was a slight tendency towards lower use of recommended drugs after MI in patients from Nordic, EU and other European countries as well as outside Europe compared with Sweden-born patients in the crude and adjusted models. We conducted a stratified analysis by country of birth to determine the effect of education on drug use after MI among Sweden-born and foreign-born groups separately. Neither Sweden-born nor foreign-born men showed any educational differences in recommended drug use after MI. However, poorly educated women, regardless of country of birth, used fewer recommended drugs after MI. In Sweden-born women, drug use was lower in patients with unknown, lower and middle education levels compared to those with the highest level of education (OR 0.62, 95% CI 0.46–0.83; OR 0.85, 95% CI 0.74–0.96; and OR 0.82, 95% CI 0.71–0.95, respectively). The corresponding values for foreign-born women were: OR 0.72, 95% CI 0.44–1.19; OR 0.51, 95% CI 0.34–0.77; and OR 0.65, 95% CI 0.42–1.00. Among those treated with some but not all recommended cardiovascular drugs before MI, we found a non-significant slightly lower use of drugs after MI among foreign-born compared to Sweden-born patients (men: OR 0.89, 95% CI 0.77–1.04; women: OR 0.96, 95% CI 0.82–1.12). Among those who did not use cardiovascular drugs before MI, we found a non-significant slightly lower use of drugs after MI among foreign-born men compared to Sweden-born men (OR 0.94, 95% CI 0.81–1.09). In the stratified analysis by education level, and after adjustment for age, sex, diabetes and marital status, we compared foreign-born to Sweden-born individuals. In the group with shorter duration of education, those born outside Sweden had a lower use of recommended drugs after MI among those with some but not all recommended cardiovascular drugs before MI (OR 0.82, 95% CI 0.70–0.96).

6.3 STUDY III

Downward trend in the risk of second myocardial infarction in Sweden, 1987-2007: breakdown by socioeconomic position, gender, and country of birth

Aim:

To evaluate the risk and trend of recurrent MI in Sweden in relation to country of birth, SEP, gender and age

To determine the effect of duration of residence and age at immigration on recurrence of MI

During the study period (1987–2007), we detected 117,679 fatal and non-fatal cases of second MI of which 3670 and 6151 were among women and men born

outside Sweden, respectively. In both sexes and regardless of country of birth, a decreasing trend towards increased risk of second MI was observed. The risk of second MI was 14% higher among men than women in the adjusted model as well as in the stratified analysis by country of birth. A small increase in risk of second MI was found among immigrants compared with Sweden-born patients: HR 1.07, 95% CI 1.04–1.10 and HR 1.05, 95% CI 1.02–1.09 in both men and women, respectively. In both Sweden-born and foreign-born patients who had less than 9 years of education, women had a 36% and 54% higher risk, respectively, compared to those with the highest attained level of education. The corresponding increase risks were 29% and 30% among Sweden-born and foreign-born men (see Paper III). During the study period, the risk of second MI correlated negatively with calendar year of first MI. Men born in different world regions, continents and regions had either similar or higher risks of second MI than men born in Sweden. The highest risks were found among women born in Northern Africa (HR 2.06, 95% CI 1.07–3.97) and Western Asia (HR 1.35, 95% CI 1.16–1.57). Women born in India (HR 1.84, 95% CI 1.02–3.33), Lebanon (HR 1.68, 95% CI 1.10–2.55) and Palestine (HR 2.50, 95% CI 1.24–5.00) had the highest risk. Men born in Western Europe and in the Netherlands had the lowest statically significant risk (HR 0.90, 95% CI 0.82–0.98 and HR 0.65, 95% CI 0.44–0.94, respectively). Among the African regions, men born in Uganda, Algeria and Tunisia had the highest risk (more than a 2-fold increase) and among the Asian regions men born in Palestine had the highest risk (more than 60% increase) compared to Sweden-born men. We found a positive correlation between the risk of second MI and age at the time of immigration for men, and a negative association with length of residence for both women (HR 1.20, 95% CI 1.08–1.34) and men (HR 1.17, 95% CI 1.08–1.26).

6.4 STUDY IV

Short and long term mortality after coronary artery bypass grafting (CABG) is influenced by socioeconomic position but not by migration status in Sweden, 1995-2007

Aim:

To study mortality after CABG in relation to country of birth, SEP, gender and age

During the study period (1995–2007), we documented 15,284 deaths among 72,333 patients who underwent a first isolated CABG. About 10.4% of deaths

occurred among foreign-born patients. Overall, men had a statistically significantly higher mortality risk than women after multivariable adjustment (HR 1.14, 95% CI 1.10–1.18). Regardless of country of birth and sex, patients with a low level of education had a statistically significantly higher mortality risk compared with those with longer than 12 years of education. This finding was more pronounced among foreign-born women (HR 1.53, 95% CI 1.00–2.33) (see Paper IV). There were no significant differences in the risk of early or late mortality after CABG between foreign-born and Sweden-born men and women throughout the study period after multivariable adjustment. There was a slight improvement in overall survival among foreign-born compared to Sweden-born men and women. Patients with diabetes or with missing information regarding diabetes had higher mortality than patients without diabetes (foreign-born men: HR 1.60, 95% CI 1.40–1.84; Sweden-born men: HR 1.64, 95% CI 1.56–1.72; foreign-born women: HR 1.53, 95% CI 1.24–1.88; Sweden-born women: HR 1.84, 95% CI 1.70–1.99). We found higher mortality after CABG among men born in Europe, Southern Europe, Eastern Asia and Eastern Africa compared with Sweden-born men and women. By contrast, men born in Asia and South-Central Asia, showed lower risks compared with Sweden-born patients. However, we found higher mortality risks among men born in Denmark, Bosnia and Chile, and both men and women born in China. Men born in Iran had a lower mortality risk compared with men born in Sweden. The highest risks were found in men born in Eastern Africa (HR 3.80, 95% CI 1.58–9.17), China (HR 3.61, 95% CI 1.50–8.69) and Chile (HR 2.12, 95% CI 1.01–4.47).

7 METHODOLOGICAL CONSIDERATIONS

7.1 STRENGTHS AND LIMITATIONS

All Studies are cohort studies based on national registers with high quality and validity. Strengths of the studies include the cohort design, the large sample size, and the complete nationwide coverage of incident cases of MI and of study exposures (country of birth and education level) and outcomes (incident cases of first and second MI, mortality of patients undergoing CABG and filled prescriptions after MI) and virtually complete follow-up.

Reliable demographic information about important lifestyle risk factors was lacking (all studies). This is a limitation as differences in risk profile between foreign-born and Sweden-born patients, such as higher prevalence of smoking and physical inactivity, have been observed (49, 207). There were insufficient numbers of observations for valid analyses regarding body mass index, conditions such as left ventricular function, number of diseased vessels, completeness of revascularization, indication for surgery and repeat revascularization (Study IV). Furthermore medical management after hospital discharge was not known (Study IV).

We did not classify foreign-born as either refugees or labour immigrants, which is a limitation in all studies. It has been shown that refugees have a higher risk of cardiovascular mortality compared to labour immigrants (208).

7.1.1 Misclassification of exposure

7.1.1.1 Country of birth

We do not suspect any major misclassification of country of birth due to recall bias as the register-based cohort design eliminates such bias. However, there could be some misclassification of country of birth as asylum seekers might be likely to state a country of origin for which the chance of being approved for immigration is high. However, we do not believe that this potential misclassification would affect our results to any great extent.

7.1.1.2 Ethnicity

In our studiess we used country of birth (migration status) not ethnicity. It is fobidden in Sweden to record ethnicity as it is considered as a sensitive issue. To use ethnicity or country of birth may be depend on the type of research question. For example ethnicity has been recommended for studying mental health among foreign-born. Anna-Clara Hollander explained that ‘’due to the

cultural aspects of mental health, country or area of origin is harder to interprit'' (31). A problem when using country of birth is that one country may include several ethnic groups and one ethnic group maybe presented in several countries. For example Kurdish people and Assyrians are distributed in several countries like Iraq, Iran, Syria and Turkey. They differ from other groups in these countries in many aspects including diet, cultural attitudes, and lifestyle. A study about caner and migration in Sweden has mentioned that ethnicity referes to a complex phenomena including both subjective and objective criteria it might be both theoretically and practically difficult to measure. Hence, the author has used country of birth and acknowledge the difficulties in measuring ethnicity (191).

7.1.1.3 Education level

However, we suspect some misclassification among foreign-born participants. According to our classification and Swedish standards, individuals with only compulsory school education are regarded as having a low level of education. However, in many countries having 9 years of schooling is regarded as having a high level of education. Depending on whether education is seen as a measure of SEP on a relative scale of social status or as a proxy for intellectual capacity, this could be seen as an underestimation of the education level. In this case the errors will be in one direction, i.e. highly educated persons would be classified as being less well educated. This could affect the comparison in the stratified analyses between foreign-born and Swedish-born individuals with a low education level. The foreign-born group should thus be regarded as better educated and hence are likely to have better health. It is however difficult to speculate on the magnitude if this problem.

7.1.2 Precision

The studies have high statistical precision because of their large sample size and long and virtually complete follow-up. We had enough power to stratify the analysis by age at immigration and duration of residence (Study III). This increased the opportunity to explore the effect of migration on health. However, some information on date of immigration was missing. Overall there was 12% missing information on date of immigration which varied considerably by country of birth ranging from less than 5% to 67%. The lowest level of missing information was found among those born in Latin America and Asia and the highest level was among those born in Estonia (191). We analysed duration of residence and age at immigration only among immigrants with a known immigration date; however, we do not believe that these missing data would affect our results. In our analysis of recurrent MI, mortality after CABG and drug

use after first MI we followed individuals to the date of death, date of emigration or end of study. However, it is possible that foreign-born individuals may return to their country of origin during the time of follow-up without reporting this to the Swedish authorities. Hence, we anticipate the slight underestimation of the risk of outcome to be greater among those born outside than among those born within Sweden.

7.1.3 Misclassification of outcome

We lacked information about history of previous MI events among foreign-born subjects and among those born in Sweden if the events occurred outside of Sweden. Thus, we assumed that the first record of MI in the NPR or the Causes of Death Register was the first MI. Hence, we might have misclassified some second MIs as first MIs, mostly among foreign-born patients. Likewise, some MIs that were regarded as second MIs could actually have been third MIs. Case fatality is higher after second MI than after first MI (209), and the risk of another MI is higher after the second MI than after the first MI (209). The risk of another MI is higher after the second MI than after the first (209). Therefore, this potential misclassification might induce an overestimation of the case fatality after first MI foremost among foreign-born individuals (Study I) as well as an overestimation of the risk of second MI among these patients (Study III). However, we addressed this issue (Study I) by investigating MI incidence and case fatality after MI after restricting the analyses to those free of MI for at least 8 years prior to the MI (210). The risk estimates for foreign-born and Sweden-born patients were similar regardless of which criteria for first MI were used. Furthermore, we lacked information about clinical data, such as severity and site of infarction (Study I and III), as well as medical treatment after first MI, which could have underestimated our results (Studies I and III).

7.2 BIAS ANDCONFOUNDING

True association, confounding, bias, chance and reverse causation

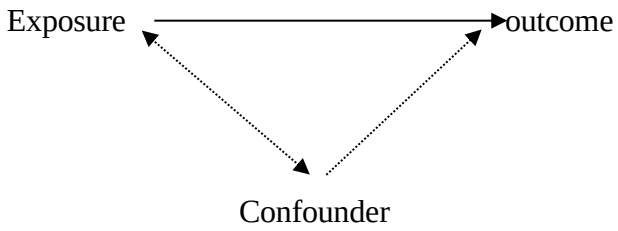
Generally in all epidemiological studies you either find an association or not. Either the association is a true association between exposure and outcome or it may be explained by ***confounding***, ***bias*** or ***chance***, or by ***reverse causality***.

Regarding the concept of *chance* (that the detected association is simply due to chance) we have computed a CI to determine where the "real" measure of a result is likely to lie (i.e. the true HR and OR). We did not have to consider the problem of reverse causation (by which instead of the exposure causing the

outcome, the outcome in fact caused the exposure) between the outcome and the exposure, as our exposure was country of birth.

Confounding

For a variable to be a confounder it must be related to the exposure of interest and it must be independently associated with the outcome.



The confounder can change the result and the direction of the association. Confounding may cause a positive association between the exposure and the outcome, or vice versa. The most common confounders in epidemiology are non-modifiable variables such as age and sex and modifiable variables such as diet, smoking habit and SEP. There are different approaches to control for confounding in epidemiological studies. For example, confounders can be controlled for in the study design phase by matching, restriction or randomization, whereas it can be controlled for in the analysis phase by stratification and multivariable adjustment. In the analysis phase of our studies we have controlled for confounders by stratification and multivariable analysis. Stratification is a commonly used method in which the analysis is performed and a measure of outcome is calculated separately for each level of the potential confounder. For example, we have stratified for sex in the analysis and adjusted for potential confounders in the multivariable adjusted models

Bias

Bias is a systematic error in an estimate (i.e. the results will be either above or below the true value), and the result of defects in the study design. Bias cannot be controlled for in the analysis. If the finding and the association results from bias, the finding is simply wrong.

Selection bias and **information bias**: these are two main forms of bias in epidemiological studies. ***Selection bias*** occurs when an unrepresentative population is selected during sampling of the study population. *Non-response* is a type of selection bias; for example, patients with the disease of interest may be more likely to respond because of their interest in the study results, or in some

circumstances they may be less likely to participate because of poor health. This type of selection bias is more common in case–control studies. By contrast, ***loss to follow-up*** is another type of selection bias which can be an issue for cohort studies; participants may drop out for a variety of reasons which could possibly bias results if the reason for leaving the study is related to the exposure or outcome of interest. We have considered this issue in our follow-up period in the design phase and in the analysis phase (see methodology section). ***Information bias*** occurs when information is collected incorrectly or inaccurately. This may result in either misclassification of outcome or exposure. ***Recall bias*** is mainly a problem in case–control studies, when cases may recall their exposure more completely than control subjects. We did not have a problem with recall bias in our studies.

Selection bias is not a common problem for cohort-based studies. To elucidate the selection bias in the current studies we should mention that migration is not a random process. Emigrants are usually self-selected from the population of their birth countries. They are from specific ethnic groups with particular socioeconomic and religious backgrounds but being healthy can also be an important factor for migration: the "healthy migrant effect" (211-214). Indeed, emigrants are often healthier than the general population that stays behind in the country of origin.

Migration is a complex process with different related reasons for migration. In general, leaving the home country and moving to new country demands considerable resources. The reasons for migration, such as health, family, occupation, education and whether or not the immigrant is a refugee have an impact on health. It is common to find a higher proportion of individuals with higher attained level of education among immigrants (215). The "healthy migrant effect" has been shown in studies of death among Turkish immigrants in Germany with lower mortality than that of native Germans (46, 55). It has been suggested that comparison should be made between immigrants and the population from their home country to study the effect of selection bias. However, this is not usually possible.

Additional points related to bias and confounding

We stratified analyses by migration status to compare some exposure for example education among immigrant groups and Swedes. We found the same effect of education regardless of country of birth but we did not have access to data for comparison with the population in the country of origin.

The age distribution is usually varied between different countries in the world as was the case for immigrant and Swedish-born populations in our studies. For that reason we have adjusted for age in all models. We have also used an age-

standardization method with the world population as the standard to adjust only for age.

In addition the trend in incidence of disease and the risk of outcomes vary among immigrants and the host population over time. Therefore we adjusted for calendar year (Studies I, III and IV). We used education as a proxy for SEP as we believe that SEP is one of the determinants of disease. We have adjusted for and stratified analyses by SEP.

8 DISCUSSION

8.1 MAIN FINDINGS

In this nationwide project from Sweden, we found that incidence of and mortality after first time MI (Study I), drug use after MI (Study II), recurrent MI (Study III) and mortality after CABG (Study IV) were influenced by country of birth (Studies I and III) and SEP. The aim of this thesis was to increase understanding of migration status and CHD incidence (Study I), outcome and prognosis (Studies I, III and IV) and management (study II, and IV). We explored the above measures in the Swedish total population with detailed information on individual country of birth.

this project is novel in that we found a less pronounced decreasing trend of first-time MI incidence among women and foreign-born individual (Study I), with no differences in drug use after MI (Study II) and mortality after CABG (Study IV). To the best of our knowledge our finding of a downward trend of second MI in Sweden is new. The risk of second MI in Sweden has not been explored previously with detailed information about country of birth. We found a higher risk of recurrent MI among men compared to women regardless of country of birth. The finding of a higher risk of second MI among foreign-born compared to Sweden born patients was also new. Furthermore a higher age-standardized rate of MI was found among immigrants in Sweden. In addition, among immigrant, we observed that the risk of second MI was modified by age at immigration and time spent in Sweden.

8.2 INTERPRETATION OF FINDINGS

8.3 MIGRATION STATUS

The higher incidence and worse outcome of MI among immigrants may partly be explained by the differences in lifestyle factors between immigrants and native Swedes. Along with access to appropriate medical treatment, environmental factors are also important for prognosis after MI. For example, a higher prevalence of smoking and physical inactivity, has been observed previously, which might explain some of the increased risk found among certain groups of immigrants in our study (49, 207, 216, 217). In particular, a high prevalence of physical inactivity among immigrant women has been shown (49, 217, 218). Previous studies have found differences in risk factor patterns of CHD between immigrants in Sweden (11, 207, 219). A higher prevalence of hypertension and the highest mean cholesterol values were found among Finnish immigrants in Sweden (207, 220). Finnish and Turkish

immigrants have the highest age-adjusted risk of diabetes (11, 49). A higher prevalence of obesity among women born in Turkey, Iraq, Bosnia, Finland, South Europe, Chile and South America compared to women born in Sweden has been reported previously (191, 221, 222). Furthermore, migration itself is a stressful process, with individuals subject to many pressures and anxiety. It has been highlighted that migration can have a negative influence on immigrant health, especially with regard to anxiety and depression (50, 51). The higher incidence of first-time MI among some immigrants in Sweden is likely to partly be explained by severe mental stress such as post-traumatic stress disorder among those born in Serbia and Bosnia (53). After the Bosnian civil war, a large number of refuges came to Sweden, and a high prevalence of common anxiety disorders, as well as post-traumatic stress disorder have been reported among immigrants born in Serbia and Bosnia.

The migration process (223) involves many changes such as separation from friends and relatives, language, culture, contact and loss of social status (38) which may cause migration stress that influences health behaviours (e.g. physical inactivity, smoking and obesity) as well as CHD risk factors (e.g. high cholesterol, diabetes and hypertension) (49, 207). In addition, the incidence of CHD depends on the country of origin (52). Immigrants born in Europe had a very similar incidence of MI compared with native Swedes. This could in part be due to similarities in lifestyle factors and that immigrants from Europe may cope with a new life in Sweden more easily than non-European immigrants, as they might better understand the Swedish culture, norms and society. All this could lead to a better integration with less stress.

In some settings it has been shown that emigrants are a selected group who are healthier than who stay behind in the country of origin (46, 54, 55). In general, immigrants are made up of a mixed group of different population subgroups depending on the countries of origin as well as subjects with different reasons for immigration. With regard to the "healthy migrant effect", immigrants may have a lower risk and incidence of MI than people in the host country. However because in general migration is a stressful process, a higher incidence and risk of MI among immigrants might be expected. In both cases, from an equity perspective, we should aim to minimizing the differences between immigrants and host populations and further try to decrease the incidence of MI for the whole population. Therefore our findings of a difference, albeit small, in CHD outcomes between immigrants overall compared to Swedes but still of value for the Swedish health care system. We did not compare the incidence and outcome of CHD between immigrants in Sweden to those who stayed behind in their country of origin. However, a majority of immigrants in Sweden have been

found to have better outcome of CHD compared to those in their country of birth (47).

In addition, moving to a new social and cultural environment may modify the behaviour and CHD risk factors that the immigrant brings from the country of birth. A favourable adoption process to the Swedish dietary habits after migration among Iranians living in Sweden was found compared to Iranians living in Iran (224). In another study it was found that migration from Finland to Sweden was associated with adopting new healthy dietary habits, but on the other hand losing other healthy dietary habits (225). We explored the effect of acculturation by studying the risk of second MI by age at the time of immigration and length of stay in Sweden. The lower risk of second MI among immigrants with longer duration of residence in Sweden observed in our study may reflect multiple factors, such as better command of the Swedish language with corresponding increased trust in, knowledge of and utilization of the healthcare system and improved compliance with medical interventions, including pharmacotherapies, smoking cessation dietary interventions and other treatment programs. The positive effect of length of stay has previously been investigated with regard to the risk of first MI among immigrants living in Sweden (8). Our findings of a downward trend in case fatality after first MI and risk of second MI over the last two decades among immigrant in Sweden is in line with observations in the Northern Sweden MONICA study from 1985 to 1998 (226) and in the total Swedish population up to 2001(226, 227) as well as in Finland (228, 229). The finding is partly due to better primary and secondary prevention (229).

Instead of finding that neither short-nor long-term mortality after CABG was influenced by migration status in Sweden we would probably see to a lower risk among immigrants if were able to adjust for unmeasured life style factors such as smoking as we expect smoking, to be more common among foreign-born than among Sweden-born men (49, 207). We found no significant differences in drug use after MI by migration status in contrast to the findings of one recent study of lower use among foreign-born individuals (27). However, the authors did not take into account drug use before MI; hence our study is not confounded by access to primary prevention. In addition, we investigated the combination of recommended drugs after MI not only single drug use.

That we found no differences in drug use after MI or in mortality after CABG could party be explained by the universal Swedish health system and by the fact Sweden is a welfare state with relatively low health inequity (230, 231). But the finding of equal drug use still may not reflect health equity and equality in access to health care in Sweden. If we expect some immigrant groups to have a higher prevalence of hypertension and hypercholesterolaemia (207, 220), greater use of

ACE inhibitors and lipid-lowering agents would be predicted in Finnish immigrants compared to Swedish-born individuals

8.4 SEP AND GENDER

The inverse association between SEP and MI incidence, risk of second MI and CABG mortality are in line with the findings of other studies (14, 15, 19, 22, 67-74, 84, 91, 210, 232-236). Similarly, in line with our results, studies have shown under-prescription of drugs in lower SEP groups in Sweden and worldwide (25, 27, 67-74, 237, 238). Women and immigrants with low SEP had a higher risk of second MI (Study III). This impact of education could possibly be explained by the effect of lower use of medication (24, 27, 239) and access to revascularization procedures (86, 240). Furthermore, patients with a low SEP may be less likely to agree to cardiac interventions (241). Also, the prevalence of high cholesterol, hypertension, smoking, and other classical MI risk factors is higher in individuals with a low SEP (87-89).

The incidence of MI continues to decrease in both sexes regardless of country of birth. Recently, among women, the risk has been decreasing at a slower rate than for men. The prevalence of smoking may explain this observation. Smoking has historically been higher in men than women (89) but this seems to be changing towards higher prevalence in women and decreasing prevalence in men (199). We observed a slight increase in first-time MI incidence around the year 2001. The change in incidence can be explained by the change in diagnostic criteria of MI introduced in 2000. The new criteria have focused on troponin T concentrations combined with other factors. According to the new criteria of MI in 2000, cases with acute coronary syndrome that had been diagnosed as having unstable angina are now categorized as having myocardial infarction (242).

9 CONCLUDING REMARKS AND FUTURE PERSPECTIVES

- Our finding of inequalities in incidence of MI and health outcome after MI (second MI) by country of birth is in accordance with the results of the majority of previous studies in Sweden. Poor coronary heart disease (CHD) health was found among some groups of immigrants, in particular among foreign-born women. Hence, public health policy should focus more on the health of migrants. Furthermore, immigrants with the highest risk of disease and poor health outcome should be targeted.
- The risk of a second MI among immigrants tended to be more similar to that among Sweden born. Such observations gives a hint on the environmental influence on the CHD risk. Our findings support the hypothesis that acculturation measured by the time spent in the host country may have a positive influence on immigrant health (given the incidence in the host country is lower than in the country of origin)
- Our findings do not support those of previous studies showing that drug consumption after MI is influenced by country of birth in Sweden. However detailed information about indications for medication, comorbidities and risk factors among individuals is necessary in order evaluate health equity with regards to drug consumption after MI.
- Our findings support the idea that universal health insurance and coverage has a positive impact on diseases and health outcomes. No difference in early and late mortality after CABG was found between immigrants and Sweden-born patients. However, further research is needed to include more information regarding severity of disease, comorbidities and risk factors.
- Despite the decreasing trend in incidence of CHD and improvement in the prognosis and management, a low level of education as a measure of poor SEP remains an important risk indicator for all outcomes in our study. This needs further investigation.
- The concepts of migration, SEP and gender are complementary to each other. Research regarding migration and health is not complete without considering each of these factors.

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11 SAMMANFATTNING PÅ SVENSKA/ SUMMARY IN SWEDISH

Bakgrund: Hjärt-kärlsjukdom med framförallt akut hjärtinfarkt är en av de stora folksjukdomarna. I Sverige står cirkulationsorganens sjukdomar för cirka 50 procent av all dödlighet varav hälften är hjärtsjukdom. Ungefär 16 procent av befolkningen i Sverige är utlandsfödd. Etniska skillnader i sjukdomsförekomst och prognos efter sjukdom har visats förekomma i stora delar av världen. Syftet med denna avhandling är att öka kunskapen om skillnader i sjukvårdsutnyttjande efter hjärtsjukdom genom att studera insjuknande och återinsjuknande i hjärtinfarkt, läkemedelsanvändning efter hjärtinfarkt, och prognos efter hjärtinfarkt och efter by-pass-operation i relation till födelseland, socioekonomisk position och kön.

Material och metod: Det material som används är en sammanställd databas för att studera hälsoläget hos invandrare i Sverige. Den så kallade Migration och Hälsa-databasen är en samkörning mellan ett stort antal nationella register. Studieperioderna var 1987-2008 (Studie I), 2006-2008 (Studie II), 1987-2007 (Studie III), och 1995-2007 (Studie IV). Studiepopulationen var totalbefolkningen (Studie I), alla förstagångshjärtinfarkter (Studie I, II och III) samt alla förstagångs by-pass-opererade (Studie IV). De utfall som studerats var insjuknande och dödlighet efter hjärtinfarkt, läkemedelsanvändning efter hjärtinfarkt, återinsjuknande i hjärtinfarkt, och dödlighet efter by-pass-operation. Potentiella störfaktorer var ålder, kön, utbildningsnivå, samsjuklighet, kalenderår, civilstånd och väntetid inför operation. Vi beräknande incidensrat (IRR), hazard ratio (HR) (Studie I, III, IV) och oddskvot (OR) (Studie II) med 95 procentiga konfidensintervall (95 % CI) i multivariata modeller genom Poisson, Cox, och logistisk regression.

Resultat: En nedåtgående trend i insjuknande i förstagångshjärtinfarkt och i dödlighet efter 28 dagar i hjärtinfarkt sågs för båda könen oavsett födelseland. Dock var minskningen över tid något större för kvinnor och för utlandsfödda. Bland de som inte hade adekvat hjärtmedicinering innan hjärtinfarkt hade utlandsfödda något mindre användning av rekommenderade läkemedel efter hjärtinfarkt i den justerade modellen (OR 0,92 95 % CI 0,83–1,03). Bland de med lägst utbildningsnivå hade utlandsfödda något lägre användning av rekommenderade läkemedel jämfört med svenskfödda. Kvinnor med låg socioekonomisk position hade lägre användning av läkemedel jämfört med män oberoende av födelseland (Studie II). En nedåtgående trend i risken att återinsjukna i hjärtinfarkt observerades. Män hade oberoende av födelseland en högre risk för återinsjuknande i hjärtinfarkt än kvinnor (HR 1,14 95 % CI 1,12- 1,55). Utlandsfödda hade en något högre risk än svenskfödda. Utlandsfödda som bott i Sverige kortare än 35 år hade en högre risk än de som bott längre än 35 år (Studie III). Vare sig bland män eller bland kvinnor var det någon skillnad mellan utlandsfödda eller svenskfödda i dödlighet på kort eller lång sikt efter by-pass-operation. Dock skilde sig dödligheten åt mellan födelseland och var högst för födda i östra Afrika (HR 3,80 95 % CI 1,58–9,17), Kina (HR 3,61 95 % CI 1,50–8,59), och Chile (HR 2,12 95 % CI 1,01–4,47). Patienter med låg utbildningsnivå hade högre insjuknande i hjärtinfarkt och sämre prognos efter hjärtinfarkt och by-pass-operation jämfört med de med utbildning längre än 12 år oberoende av kön och födelseland (Studie I, III, och IV). Denna skillnad var tydligare bland utlandsfödda kvinnor.

Slutsats: En något ökad risk för insjuknande i och dödlighet efter förstagångshjärtinfarkt och en ökad risk för återinsjuknande i hjärtinfarkt sågs hos utlandsfödda jämfört med svenskfödda. Även om insjuknande och dödlighet efter förstagångshjärtinfarkt och risk för återinsjuknande i hjärtinfarkt har fortsatt att minska över tid så har de med låg socioekonomisk position, mätt som låg utbildningsnivå, oberoende av födelseland och kön alltjämt en ökad risk för dessa händelser. Ingen uppenbar skillnad mellan utlandsfödda och svenskfödda i användning av rekommenderade läkemedel efter hjärtinfarkt kunde ses. Det var ingen skillnad i dödlighet vare sig på kort eller på långsikt efter by-pass-operation mellan utlandsfödda och svenskfödda. Dock visar skillnaderna i adekvat sekundärprevention efter hjärtinfarkt på ojämlikhet i vård mellan personer med olika utbildningsnivå oberoende av födelseland.

12 PUXTE/ SUMMARY IN KURDISH

Nexoşî dil w lulekanî xwén (cardiovascular diease CVD) kéşeîekî serekî biwarî tendirustîye le cîhanda. Be péyî raportî salaneî rékxirawî tendirustî cîhanî (WHO), le salî 2010 nizîkeî 17 milîon mirdin tomar kirawe be hokarî nexoşîyekanî dil (CVD), le néwan ew mirdwaneşda nizîkeî 7 milîon hokarî mirdinyan nexoşî lule xwénberakanî koronerî biwe, wate nexosî ew xwénberaneî ke xwén bo dil deben (Coronory heart disease, CHD). Cégeî amaje pé kirdine ke le wilatî Swîd, salane réjeyekî zor le serheldanî (Incidence) nexoşîyekanî dil, w mirdin (Mortality) be hokarî nexoşî dil tomar dekrét. Be şéweyekî giştî rudanî nexoşî celdeî dil (Myocardial infarction, MI), le hemu corekanî nexoşî dil bawtire le néwan mirovî pègeîştu (Adult).

Dil weku hemu endamekanî tirî leş péwîstî be xwén w oxigîn heye. Katék xwén be şéweîekî asaîy nagate masulkekanî dil, ewa mirov tuşî nîşanekanî nexoşî dil debét. Le ruî zanistî şanezanîyewe hokarekanî degretewe bo kelekebunî çewrî w rîşalî faîbrîn le naw lule xwénekani koronerîda yan piçranî (rupture) ew girmoleî (Atherosclerotic plaque) ke dirust buwe ke lewaneye bibéte serheldanî celdeî dil yan bibéte hoy mirdinî nexoşe tuşbuweke.

Hokarekanî nexoşî dil ewaneî taku ésta zanrabin bo nimune: (temen, hokarî bomaweyî, regez w nejad), em hokarane hokarî negorin. Hokarekanî dike be hokare gorawekan denasrén çunke mirov ta radeyek detwanè beseryanda zal bét, bo nimune: (pestanî xwén, çewrî, cigerekéşan, nexoşî şekre, qelewî w werjiş nekirdin e legel hokare derunîekan).

Be péî twéjinewe zanistîyekan be şéweyekî giştî réjeî tuşbun be nexoşîyekanî dil le néw penahendekanda (Immigrants) ziyatire be berawerd legel ewaneî le dayik buî wilateken. Wek zanirawe réjeyekî zor le xelkî le dayikbuî dereweî wilat (Foreign-born) le wilatî Swîd dejîn ke réjeyan degate nizîkeî (16 %) î komelgeî Swîd.

Ème le wilatî Swîd le zankoî Karolinska (Karolinska Institutet), wek çend twéjerék le biwarî pizîşkî nexoşîyekanî dil, lèkolînewemaan le ser le dayikbuwanî dereweî wilat ke le Swîd dejîn encam da. Le encam da, boman derkewt ke réjeî rudanî nexoşî celdeî dil be şèweyekî giştî ruî le kembun daye le néwan ewaneî le Swîd le dayikbun w le dayikbuwanî dereweî Swîd. Belam em diyardeî kem bunewe kemtir bedî dekrét lenéwan xanime le dayikbuwekanî dereweî Swîd. Egerî rudanî celdeî dil (MI) w dubare buneweî (second attack of MI) le néwan le dayikbuwanî dereweî wilat zîatire be berawerd legel ewaneî le Swîd le dayik bun.

Paş twéjîneweî zîatir boman derkewt ke egerî mirdin le dwaî encamdanî neştergerî xwènberekanî koronerî (coronary artery bypass graft) hiç cîawazîyekman bedî nekird le néwan le dayikbuwanî nawewe w le dayikbuwanî dereweî Swîd, herweha réjeî wergirtinî derman w çareser cîawaz nebun le nèwan ew du girupeda. Legel eweş da le hemu twéjînewekanda boman derkewt ke ewaneî ast w pileî xwèndinîan nizme zîatir tuşî ew nexoşîyane debin. Herwaha egerî mirdin be hoy nexoşîyekanî dil w neştergerî péwend bew nexoşîyane le néwanyanda zîatire. Sereraî eweş be réjeyekî kemtir çareser w derman wer degrin bo ew nexoşiyane be berawerd le gel ewaneî ke pileî xwéndewarîyan berz tire.

Zanîn w peîrew kirdinî rénimaîye tendirustîyekan be hengawékî giring dadenrét bo xo parastin le tuşbun w egerî mirdin bem nexoşîye. Encamekanî em twéjîneweye agadarkirdineweyeke bo hawwilatîyanî le dayikbuî dereweî Swîd w herweha bo sîstemi tendirustî Swîd. Lékolînweî zîatir péwîste bo bedwaçunî hokarekan bo eweî bizanirét ke boçî derencamekanî em twéjîneweye cîawaze le néwan hendék le le dayikbuwanî dereweî wilat be berawerd le gel le dayikbuwanî Swîd w le néwan ewanî ke pileî xwéndinyan nizimtire (herdu giropî le dayikbuwanî derewe w naweweî Swîd).

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